Current opinions in renovascular hypertension

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Renal artery stenosis and renovascular hypertension are important considerations in patients with hypertension that is difficult to control. The diagnosis may also have prognostic significance for progressive renal disease. The most common causes of renal artery stenosis are atherosclerotic disease and fibromuscular dysplasia. The pathophysiology of renal artery stenosis is reviewed, and the pros and cons of various imaging studies in the appropriate clinical setting are discussed. Treatment includes aggressive control of hypertension, dealing with associated cardiac risk factors, and angioplasty or surgery in specific circumstances.

Renovascular hypertension (RVH) is defined as the presence of systemic hypertension due to a stenotic or obstructive lesion within the renal artery. It is a form of secondary hypertension, accounting for an estimated 0.5% to 4% of cases in unselected hypertensive patients (1–4). However, the simultaneous presence of renal artery stenosis (RAS) and systemic hypertension should not lead to the conclusion that the patient has RVH; strictly speaking, the definitive diagnosis of RVH can only be made retrospectively when hypertension improves upon correction of the stenosis.

Renovascular disease may lead to RVH as well as ischemic nephropathy, an increasingly recognized cause of end-stage renal disease in the US (5). The optimal treatment of RVH remains a matter of considerable debate. Accordingly, it is valuable to review the current evidence regarding this important cause of secondary hypertension.

ETIOLOGY

The two most common causes of RVH are atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD). Obstruction may arise from the renal artery wall, such as in dissection, vasculitis, and neurofibromas, or from extrinsic compression, such as by a tumor. Embolism and diversion of blood flow by arteriovenous malformations can also compromise renal perfusion, leading to RVH.

Ninety percent of cases of RVH are due to ARAS. It occurs mainly in older men, with the lesion at the ostium or proximal third of the renal artery as an extension of an aortic plaque. It is bilateral in approximately one third of cases. Risk factors for the development of ARAS are identical to those associated with systemic atherosclerosis, i.e., advanced age, male sex, smoking, diabetes mellitus, hypertension, positive family history, and dyslipidemia. It is generally believed that ARAS slowly progresses over time, but the rate of progression is variable.

Ten percent of cases of RVH are due to FMD (6). FMD is a collection of noninflammatory vascular diseases that affect the intima, media, and adventitia, with the medial fibroplasia form being the most prevalent (7). It is found mainly in younger women. Bilateral renal artery involvement with extension into the distal portion of the artery and its branches is common.

PATHOPHYSIOLOGY

Pioneering work on RVH was done by Goldblatt et al in the 1930s. They studied the effect of unilateral and bilateral renal artery clamping on dogs (8). This pathophysiologic model served as the basis for future studies. Extrapolating from the laws of fluid dynamics, the blood flow in the renal artery is inversely proportional to the resistance in the vessel, which in turn is related to the fourth power of its radius. Hence, we see that the radius is the most critical factor in determining the amount of blood flowing through the vessel, and that a change in luminal patency from 80% to 90% results in a much more significant reduction in renal blood flow than a change from 30% to 40%. It is widely believed that the obstructing lesion in the renal artery has to reach a "critical level" of about 75% to cause any clinically significant hemodynamic effects.

The proposed mechanism of the generation of systemic hypertension is shown in the *Figure.* In the case of bilateral RAS, or unilateral RAS in a functionally impaired or absent contralateral kidney, the increased renin produced by both kidneys is responsible for the increased salt and water retention and subsequent

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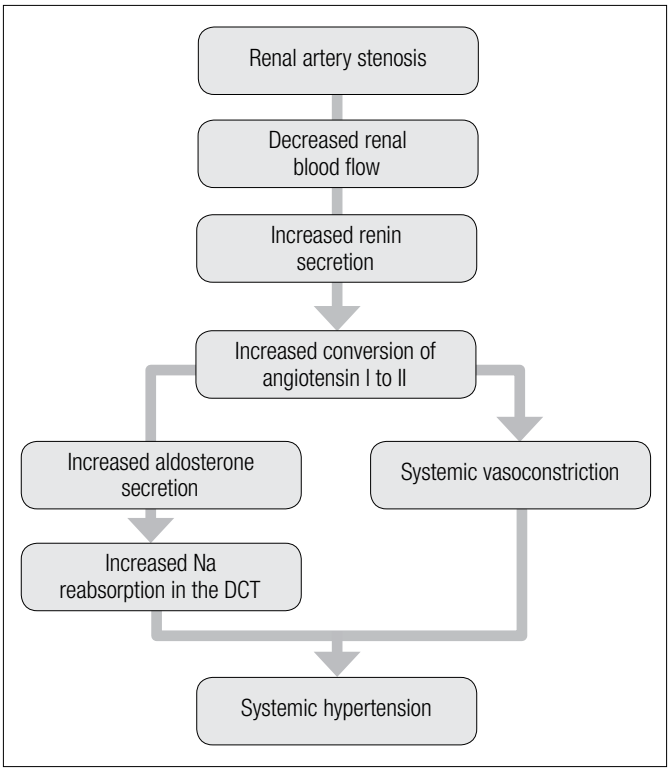

Figure. Mechanism of systemic hypertension caused by renal artery stenosis. NA indicates sodium; DCT, distal convoluted tubule.

hypertension. In the case of unilateral RAS with a normal contralateral kidney, hypertension is caused by the increased renin produced in the ischemic kidney while the nonischemic kidney has its renin production suppressed (9, 10).

DIAGNOSTIC APPROACHES TO RENOVASCULAR HYPERTENSION

As mentioned previously, the mere presence of RAS and hypertension does not establish the diagnosis of RVH. A three-step approach to the diagnosis of RVH has been suggested (11). The first step is an appropriate selection of patients who are more likely to have RVH. The clinical factors associated with RVH are described in the *Table* (6, 11, 12). Second, the patients' renal arteries are imaged to demonstrate RAS. Finally, resolution or improvement in blood pressure control occurs with reversion of the stenosis.

IMAGING TECHNIQUES

The gold standard for the imaging of renal arteries is a conventional renal angiogram with a low-osmolar contrast agent. However, this test is invasive and carries the risk of contrast-induced nephropathy. Hence, it is not used routinely unless concurrent therapy with angioplasty, with or without stenting, is being considered.

Digital subtraction angiography (DSA) uses less dye than a conventional arteriogram but is still invasive. In addition, the quality of images with DSA is not as good as with conventional angiograms.

Captopril-enhanced renography and scintigraphy offer a noninvasive test and the ability to assess renal functional status.

Table. Clinical findings associated with renovascular hypertension (6, 11, 12)

Hypertension
Abrupt onset or sudden worsening of well-controlled hypertension
Refractory to medical treatment with more than three drugs
Age and sex (young women are suggestive of FMD; older men are suggestive of ARAS)
Malignant or accelerated hypertension
No family history of essential hypertension
Renal factors
Azotemia induced or worsened by antihypertensive medications, in particular ACE inhibitors or ARBs
Unexplained azotemia
Discrepancy in kidney sizes by more than 1.5 cm with cortical scarring (for unilateral RAS)
Bilateral small kidneys with cortical scarring (for bilateral RAS)
Low-grade proteinuria with bland urinary sediment
Other associated findings
Laboratory evidence of persistent RAAS activation, such as chronic hypokalemia
Abdominal or flank bruit or both on physical examination
Unexplained CHF symptoms or "flash" pulmonary edema
Evidence of systemic atherosclerotic vascular disease (e.g., CAD, PAD, AAA)
Smoking
Severe retinopathy
Left ventricular hypertrophy

AAA indicates abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; ARAS, atherosclerotic renal artery stenosis; ARBs, angiotensin II receptor blockers; CAD, coronary artery disease; CHF, congestive heart failure; FMD, fibromuscular dysplasia; PAD, peripheral arterial disease; RAS, renal artery stenosis.

However, their use is limited in patients with bilateral RAS and in patients with significant renal insufficiency. They provide a basis for functional, not anatomical, diagnosis of RAS, as there is no direct visualization of the renal arteries.

Duplex ultrasound imaging allows direct visualization of the renal vascular tree while assessing blood flow velocity and pressure wave forms (13). Limitations include interoperator variability and the need for expertise in obtaining and interpreting the images.

Spiral computed tomography angiography enables a three-dimensional reconstruction of the vascular tree and has excellent sensitivity and specificity to visualize RAS. However, it requires up to 150 cc of iodinated contrast, which may be nephrotoxic.

Magnetic resonance angiography (MRA) is another noninvasive imaging technique and results in excellent visualization of the renal vasculature. Gadolinium is used as the radiocontrast in the phase contrast technique. Drawbacks include the high cost of MRA and the potential for nephrogenic systemic fibrosis in patients with renal insufficiency (14).

THERAPEUTIC APPROACHES TO RENOVASCULAR HYPERTENSION

Treatment options in patients with RVH include pharmacological therapy with various antihypertensive medications, percutaneous angioplasty with or without stent placement, and surgical revision of RAS. The availability of potent antihypertensive drugs and the advances in endovascular techniques, as well as stents, have made surgical treatment rarely necessary.

In patients with FMD, percutaneous angioplasty is the treatment of choice, often resulting in relief of the stenosis and marked improvement (or cure) of the hypertension (8). Stents may be used in patients with suboptimal results with angioplasty alone (15, 16). Surgery is considered to be the last option, particularly for patients for whom endovascular procedures have failed (17).

Despite the relative frequency of ARAS and numerous previous studies examining different treatment options, there is no general consensus among physicians on the ideal therapy for this condition. Numerous randomized prospective studies have found no evidence of improvement in blood pressure control in patients undergoing angioplasty over medical therapy alone (18–20). The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study randomized 106 patients with hypertension and ARAS either to undergo percutaneous transluminal renal angioplasty or to receive drug therapy. At 12 months, there were no significant differences between the angioplasty and the drug therapy groups in systolic and diastolic blood pressure, daily drug doses, or renal function (18). In the Essai Multicentrique Medicaments vs Angioplastie (EMMA) study, patients were randomly assigned to antihypertensive drug treatment (control group, n = 26) or angioplasty (n = 23). The investigators did not find differences in blood pressure at 6-month follow-up (20). The Scottish and Newcastle Renal Artery Stenosis Collaborative Group randomized 55 patients with ARAS to angioplasty versus medical therapy alone. In patients with bilateral RAS randomized to angioplasty, a statistically significant lowering of blood pressure was observed at the latest follow-up (range, 3–54 months). The mean fall in blood pressure at the latest follow-up in the angioplasty group, corrected for the medical group response, was 26/10 mm Hg (19). Interestingly, two meta-analyses of these studies, each with 210 patients, both found a significant improvement in blood pressure with angioplasty compared with medical treatment (21, 22).

One of the largest trials, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study, included 806 renal failure patients (mean serum creatinine approximately 2 mg/dL) with atherosclerotic renal vascular disease from 54 medical centers in the United Kingdom and four medical centers in Australia and New Zealand. They were randomized to receive either revascularization and medical therapy or medical therapy alone. On average, patients had 75% RAS. At 1-year follow-up there were no differences in the change in serum creatinine level (it rose by 0.2 mg/dL in both groups) or in rates of renal events, including acute renal failure. There were no statistically significant differences in blood pressure, kidney function, rates of myocardial infarction, cerebrovascular events, or hospitalization due to angina, heart failure, or the need for percutaneous coronary intervention or bypass surgery between the intervention and medical therapy groups (23).

Currently, at least three major studies are under way to help decipher optimum treatment for patients with ARAS. The STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery (STAR) study aims to compare the effects of renal artery stent placement together with medication versus medication alone on renal function in 140 ARAS patients (24). Medication consists of statins, antihypertensive drugs, and antiplatelet therapy. Patients are to be followed for 2 years with extended follow-up to 5 years. The primary outcome of this study is a reduction in creatinine clearance of more than 20% compared with baseline. A trial looking at cardiac endpoints, the stenting of Renal Artery Stenosis in Coronary Artery Disease (RAS-CAD), is a randomized study aiming to recruit 168 patients at a single institution. It is designed to study the effect of medical therapy alone versus medical therapy plus renal artery stenting on left ventricular hypertrophy progression (primary endpoint), and cardiovascular morbidity and mortality (secondary endpoints), in patients affected by ischemic heart disease and RAS (25). The Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study is a National Institutes of Health–funded multicenter trial testing the hypothesis that stenting atherosclerotic RAS in patients with systolic hypertension reduces the incidence of cardiovascular and renal events (26, 27). The CORAL study has completed enrollment with over 900 patients, but results will not be available for some time.

At this time, there is no clear benefit of revascularization for ARAS, especially in patients for whom blood pressure can be controlled easily and who have no evidence of ischemic nephropathy. The risks of the procedure may outweigh any potential benefits. Angioplasty with or without stenting may be of benefit in patients with hypertension that is difficult to control in the setting of decreased renal perfusion, because uncontrolled hypertension is a major cardiovascular risk factor. Accordingly, aggressive treatment of hypertension with medications is recommended. Antihypertensive treatment may also include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), provided that renal function is stable and that close follow-up is available. Van de Ven et al studied the effects of controlled exposure to ACE inhibitors on plasma creatinine in 108 patients at risk of severe bilateral ARAS (28). Serum creatinine was closely followed and the offending ACE inhibitor stopped in those with a rise in creatinine of more than 20%. Indeed, creatinine did rise in 62 patients, but no case of acute renal failure was encountered, and plasma creatinine always improved after stopping the ACE inhibitor, emphasizing their safety in RAS. Medical therapy should also include statins to prevent further progression of atherosclerotic plaques in the renal arteries and cardiac prophylaxis with low-dose aspirin in patients with ARAS. However, prospective trials

confirming this benefit are still lacking. Smoking should be strongly discouraged.

SUMMARY

RVH is an uncommon but potentially remediable cause of hypertension. ARAS and FMD are the most common causes of RAS. In a select group of patients with certain clinical clues, imaging is indicated for diagnosis. Appropriate treatment continues to evolve, but control of hypertension is imperative. The role of angioplasty is well accepted in FMD but is not so clear in ARAS.

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